INHERITANCE OF CANCER IN MICE

DR. LEO LOEB

THE DEPARTMENT OF COMPARATIVE PATHOLOGY, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, ST. LOUIS

IN the following we shall give a summary of our investigations into the part heredity plays in the origin of cancer. Our interest in this problem dates back a considerable number of years. In 1899, in conjunction with Dr. Jobson, we made our first observations on the endemic occurrence of cancer at the Stockyards in Chicago. At that time we found cattle coming from a certain ranch in Wyoming especially prone to have cancer at the inner canthus of the eye (1). A few years later we observed an endemic occurrence of sarcoma of the thyroid in a family of rats. In this case we pointed out that the circumstances under which these sarcomata originated pointed to a hereditary condition rather than to an infection. At that time (1904)[1] we referred to the desirability of investigating experimentally this endemic occurrence of cancer (2) and we had particularly in mind an analysis of the etiological factor in breeding establishments of mice or rats. Such an opportunity presented itself a few years later in the breeding establishment of Miss Lathrop in Granby, Mass. A preliminary investigation here revealed the fact that cancer occurred with much greater frequency in certain inbred strains than in others, and that no indications whatever could be found of cage infection or direct infection from animal to animal. We concluded in 1907 on the basis of these observations that there existed a hereditary predisposition which was responsible for the endemic occurrence of cancer (3). At that time we planned further much more extensive experiments on the mode of hereditary transmission of cancer in following isolated families and strains of mice through several generations and in study-

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ing the effect of hybridization on the cancer rate. This was made possible to us in 1910 through the interest which Miss Lathrop, who bred a very extensive stock of mice, took in these plans and with her cooperation we carried out these breeding experiments from 1910 on through a considerable number of years. In the following year we published the record of a cancer family of mice which we had observed through several generations (4). Altogether we carried out observations on approximately 12,000 female mice reaching the cancer age which we followed throughout the whole period of their life and which were observed through successive generations. Many of them were used for hybridization.

In the meantime E. E. Tyzzer had published in 1907 and subsequently studies of the inheritance of cancer in mice (5). This author found indications that heredity may play a part in the etiology of animal cancer. Somewhat later Murray undertook similar studies in which he used methods similar to those previously employed in the study of human cancer. This author compared the frequency of cancer among individuals whose mother or grandmother had cancer on the one hand, and among those in whom cancer had not been observed in the direct ancestry but may have occurred in the great grandparents (6). Murray found on the average about 20 per cent. of cancerous mice among those whose direct ancestors had suffered from cancer and 11 per cent. among those whose direct ancestry had been free from cancer. In certain age classes the cancer rate of both kinds of mice showed only a very slight difference and in one age class the cancer rate was even higher in those whose direct ancestry had not been affected by cancer.

These results as well as our previous studies and some occasional observations of Albrecht and Hecht and of Spronk and a few others made very probable the significance of heredity in the etiology of cancer.

Nevertheless there were opposing views such as those of Borrel and others who referred the endemic occurrence

of cancer not to heredity, but to infection, and as late as 1910 Bashford expressed the opinion that heredity has no significance in the causation of cancer.

We believe that our investigations which were carried out with the cooperation of Miss Lathrop established the importance of heredity in the etiology of cancer beyond doubt, and they point more accurately to the mode of inheritance and the interaction between heredity and other factors (7). Subsequently Miss Maud Slye began to use a large stock of mice which she had collected for biological purposes for a similar study of heredity of cancer in mice (8). While in general her conclusions as to the significance of heredity in cancer agree with ours and are thus confirmatory of ours, she has extended her researches in various other ways and has made valuable contributions. In regard to certain questions our conclusions differ. To those we shall have occasion to refer in the following pages.

The following is a summary of our main conclusions:

1. The cancer rate of each strain of family is a definite characteristic of this strain and is transmitted by heredity to successive generations. The differences in the tumor rate in various strains are very pronounced; the tumor rate may vary between zero in certain strains and almost 100 per cent. in others. All intergrades may be found. To cite a few examples of tumor rates of various strains: English 67.6 per cent., European + I daughter of No. 10 72 per cent., 344 + 328 = 79 per cent., London 28 per cent., No. 8 27.5 per cent., 8 + German 34 per cent., Cream 5.9 per cent., European 9 per cent., German + 8 0 per cent. (344 + Black Cream) + Cream 0 per cent.

While these strains represent composites, they are on the whole in so far homogeneous, as in the large majority of cases substrains showed similar tumor rates. Thus in the case of the English and Cream, for instance, numerous substrains showed the typical tumor rates. In a number of cases individual families were separated and followed, and on the whole their tumor rate agreed very

well with that of the main strain. Certain deviations must of course be expected in the case of relatively very small numbers of individuals obtained in case of an individual family or small substrains, and yet quite frequently even small substrains or families agree in their tumor rate with the main strain.

We may give some examples of the comparative tumor rates of the main strains and of the substrains: The strain $8\frac{1}{2} + 328$ had a tumor rate of 56.4 per cent. There was among them a family No. 1075 consisting of ten females reaching an age which permitted inclusion in these records. They had a tumor rate of 60 per cent.; another family of this strain (No. 1,113), consisting of sixteen such females, had a tumor rate of 88 per cent. Family 782*a* (22 females) had a tumor rate of 68 per cent. Among the substrain English Sable which had in the corresponding generation an average tumor rate of 75 per cent., there was a family No. 437 (27 females) with a tumor rate of 89 per cent. The same correspondence is found in others and among them low rate strains. In certain cases, however, certain substrains of families can be split off which differ in their tumor rate. Thus at an early period of inbreeding there were split off from the English strain two substrains with low rates: English Silver and English Silver Fawn, with tumor rates of 8 per cent. and 12 per cent., respectively.

From the strain London (tumor rate 28 per cent.) two families were branched off which showed very different rates: London Blue and White (31 females) 55 per cent., and Family 481 (25 females) 0 per cent. But these are not the usual occurrences. A correspondence between main strains, substrains and families is the usual finding.

We see then that all kinds of intergrades in the tumor rates occur in different strains, substrains and families and that these are on the whole constant and characteristic of strains and families.

2. These differences in rate persisted through successive generations in the majority of our strains with a sur-

prising regularity. Thus for instance, in the strain London, the earlier generations (120 female mice) showed a tumor incidence of 27 per cent., in the intermediate generation (61 females) the figure was 38 per cent. and in the later generation (197 female mice) 28 per cent. Similar conditions were found in a number of our strains. In certain strains, however, variations in the tumor rate did occur. While some variations may of course be expected, in case the number of mice considered is very small, there occurred in addition changes which can not be attributed to this factor.

In the majority of cases in which these latter changes did occur in our stock, they consisted in a decrease in the tumor rate in later generations; in a few cases only there occurred an increase in the tumor rate. These changes were in all probability due to two factors: (*a*) In certain families and strains as a result of long continued inbreeding a gradual decrease in fertility and vigor occurred. Associated with this change was in certain cases a noticeable decrease in the tumor rate. Especially in the strain No. 8 there seemed to be a connection between loss in resistance to disease and fertility and the decrease in the tumor rate. This strain was inbred for seventeen generations and the changes in the tumor rate seemed to occur step by step in correspondence with the progress in inbreeding. Under those conditions the connection between inbreeding and change in the tumor rate appears the most probable explanation, although it can not be considered as definitely proven as yet.

(*b*) Various factors caused a selection to take place within the strain; certain families died out, while others, which happened to be more resistant to a certain disease, survived, propagated and thus gained a preponderance. These surviving families differed sometimes in appearance, or in vigor, in the behavior towards certain inoculable tumors. Such changes were accompanied in certain cases by a change in the tumor rate. In the majority of our cases a decrease occurred; in a few cases an increase;

but even in such cases the increase was moderate; there was never observed among our material a sudden transition from a low to a high rate tumor strain. The increase as well as the decrease in the tumor rate was caused by the same factor; whether one or the other should prevail depends more or less on chance, and in different material the number of strains showing the one or the other variation may be expected to differ. It has been maintained that in strains which have been inbred for a long period of time and in which a decrease in fertility occurred as the result of the inbreeding, development of cancers takes the place of the lost fertility. In inbreeding cancer replaces reproduction, as it has been expressed by Maud Slye. In our material such a substitution did not take place; in inbreeding mice vanishing fertility was not replaced by the development of cancer under ordinary conditions. Inbreeding does not lead to an increased cancer rate.

3. If we cross strains with a similar tumor rate, the offspring inherits the tumor rate common to both parents; if both parents differ in tumor rate, the tumor rate of the offspring is on the whole intermediate between those of the parents. But all degrees of intermediacy are observed. In our material the number of strains in which the rate of the parent with the higher tumor incidence dominated was on the whole greater than the contrary one.

We selected for our hybridizations especially strains which differed markedly in their tumor rate and other characteristics and which had been followed over long periods of time and had been found consistent in their behavior. The English as a representative of a high tumor rate strain and the Cream as a representative of a low tumor rate strain were especially suitable for this purpose. In the majority of cases we selected few individuals for hybridization, either one male and one female or one male and several females. We followed the offspring through several generations. The near relatives of the

individuals used for hybridization were observed as to their tumor incidence and generally found to behave in a way characteristic of their strain.

Sometimes we hybridized sisters with the same male, or we used consecutively the same male with females from strains which differed much in their tumor rate. The results in the hybrids could usually be foreseen from the known tumor rate and tumor age of the parent up to a certain point of variability. The cases in which the strains used for hybridization had a similar tumor rate could be considered as controls. Here a similar tumor incidence ought to have appeared in the offspring and this is what usually occurred.

As we stated above, the results of hybridizations are typically intermediate, but the rates and tumor ages of the crosses may in some cases approach the parent with the higher rate, in other cases the parent with the lower rate.

We shall cite two examples, where the offspring resembled the parent with the higher tumor rate. (1) A son of a tumor mouse No. 240, belonging to the strain 8 + German, was mated to a White Cream female. 8 + German was a strain fairly rich in tumors and the particular family used had a tumor rate of 43 per cent. The tumors appeared early in life. In the White Cream used in this case tumors were extremely rare and they appeared late in life. Among the offspring 9 female mice lived long enough to be included in the records. Of these 9 mice, 5 died with tumors, 1 in the first and 4 in the second age period. In this case the influence of the father is undoubtedly very marked. In the Cream strain such a tumor rate was never observed even among isolated families. The tumor age of the hybrid is, however, in this case probably affected by the mother.

(2) In the second case which we wish to mention, an English Sable male belonging to the fourth generation of English Sable, who have normally a very high tumor rate, was mated to 3 females belonging to the substrain

Cream Y. In the substrain Cream Y the tumor rate had been zero. Four generations of the offspring were observed comprising altogether 68 female mice which reached an age sufficient for inclusion in our records. Thirty-six of these mice, that is, 53 per cent., died with tumors, 11 of these in the first age period. This is a record which comes near that of the English Sable. These as well as numerous other experiments seem to us more in harmony with the conclusion that multiple factors underlie the hereditary predisposition to mammary cancer in mice than the view of Maud Slye who maintains that the factor for mammary cancer in mice is a recessive monohybrid.

(4) The age at which tumors appear is just as characteristic of individual strains as the tumor rate. The tumor age is also transmitted by heredity. In some strains tumors appear relatively early, the percentage of tumors appearing in the first age period of life comprising the first twelve months is considerably greater than in others; and this characteristic is on the whole just as constant in the strains as the tumor rate as a whole.

We can distinguish two factors in the inheritance of the tumor age: (*a*) In general in the strains with the higher tumor rates the tumors appear at an earlier period of life than in the lower tumor rate strains. This comes out very clearly when we divide all the strains into three classes, those with a tumor incidence above 40 per cent., the high tumor rate strains; those with a tumor incidence between 20 per cent. and 40 per cent., the medium tumor rate strains, and those with a tumor incidence below 20 per cent., the low tumor rate strains.

If we determine in each class the percentage of tumors appearing in the different age periods, we find that the tumors appear the earlier in life the higher the tumor incidence and the difference between the different classes is quite marked.

There is in our case a definite relation between the factors, tumor age and tumor rate. We can interpret this

relation by assuming that a certain average quantity is inherited in the individuals of different strains which determines the intensity in the tendency towards the development of tumors. This intensity may depend on the average number and character of multiple factors favoring tumor growth which is characteristic of a strain. A special kind of factors or a larger number of factors causes both a higher incidence and an earlier appearance of cancer in a certain strain.

(*b*) In addition to this intensity which is a characteristic of the strains in general, there is a peculiar tumor age in certain strains which is independent of the tumor rate. Strains with a similar tumor rate may differ in their tumor age, and in hybrids tumor rate and tumor age may be inherited separately in the offspring. Thus two of our high tumor rate strains formed by the crossing of the same male (European 151) with two sisters (first and second daughter of No. 10, respectively) with tumor rates of 72 per cent. and 54.5 per cent., respectively, have relatively late tumors, in both only 15 per cent. of the tumors appearing in the first age period. In the Cream-English hybrids the tumor rates in two strains were similar and approximately intermediate, but in one of them the tumor age approached the late one of the cream parent; in the other it was nearer the early one of the Eglish parent.

We may therefore assume that in addition to the sum total of multiple factors which determine at the same time age and tumor rate, there are special factors which determine tumor age.

5. In general the cancer rate in mice is not a sex-linked character. Either the cancer rate and age of the father or mother strain may predominate in the cancer rate of the offspring. This fact does not, however, exclude the possibility that in certain cases a sex-linked factor may enter as one of the multiple factors which in all probability determine the inheritance of cancer. Certain of our observations suggest such a possibility. We found, for

instance, that in the Cream-English hybrids the mother strain was considerably more often predominant than the father strain; in addition we found that in reversing a cross different results were obtained in accordance with the difference in the tumor rate of the mother strain. It is, however, possible that these occurrences are chance phenomena and we offered this interpretation merely as a suggestion.

6. Our investigations make it possible to express in a quantitatively definite manner the hereditary tendency to cancer in individual strains of mice, the figures varying in different strains between zero and 100. This hereditary tendency is, however, not a simple quantity, but composite, because

(*a*) The hereditary disposition to cancer is probably due to the cooperation of multiple factors. The results of hybridization, which essentially were of an intermediate character, the fact that all kinds of intergrades between father and mother strain exist and that all possible variations in the hereditary tendency to cancer exist in different strains, and that the hereditary tendency determining the cancer age is not entirely identical with the tendency expressed in the cancer rate, very strongly suggest this conclusion. Variations in the number and character of the multiple factors in the different individuals may be responsible for the variations in intensity which determine the tendency to cancer in individuals, and different strains may differ as to the mean in the distribution of the factors among the individuals belonging to the strain. Thus we may assume that the strains English, $8\frac{1}{2} + 328$, European + I daughter of No. 10 have on the average a greater number of factors than the individuals of the strain Cream and German + 8 and many others; and it would be conceivable that in many cases a tumor mouse belonging to the strain English differs from a tumor mouse in the strain Cream, the former often exceeding the minimum of factors necessary for the production of tumors.

As far as the ordinary mammary cancer of the mouse is concerned, no definite proof has so far been brought forward to support the view that the hereditary tendency to cancer is due to the presence of a simple recessive factor.

(*b*) There is hidden in the figure expressing the tendency towards the development of cancer a second factor which is variable; namely, the activity of the ovary. In all the strains the realization of the hereditary tendency to cancer presupposes the activity of the internal secretion of the ovary. Without this cooperation no cancer can originate. With the full activity of this factor the hereditarily transmitted character for intensity of cancerous tendency determines the upper limit of the cancer rate. Again the intensity of this ovarian factor can be expressed in a quantitative manner, the quantity in this case representing the time during which the ovarian internal secretion had a chance to act. If through castration in the early stages of adult, sexually mature life, at the age of three to four months, this internal ovarian secretion is eliminated in mice, mammary cancer is practically prevented from appearing even in normally high tumor rate strains. The longer the ovarian function has a chance to act, the more the cancer rate increases up to the range which is given in the figure for the hereditary tendency to cancer. While we can thus experimentally lower the cancer rate of any strain, we do not so far know of a method which would permit us to raise the cancer rate above this point. The latter is almost reached if castration occurs at the age of eight to ten months. Suspension of breeding also diminishes somewhat the cancer rate in the great majority of the cases, but to a very much less extent than the exclusion of the internal secretion of the ovary, which latter is the true realizing factor, the cooperation of which is necessary. In one strain in which through segregation of the female mice breeding had been prevented the cancer rate was even higher in the non-breeding than in the breeding mice (9). Injury to the mamilla by the suckling young which Maud Slye believed

to be the external stimulus leading to the development of cancer in mice can therefore not be an important factor in the causation of mammary cancer in this species of animals. On the other hand, our demonstration of a certain influence of breeding on the cancer rate in mice adds another, though minor, factor to the internal secretion of the ovary, which latter represents, as we stated above, the principal realizing factor. Secondary realizing factors may therefore be added to this primary factor.

In principle, conditions are probably similar to what we determined in the case of the typical mammary cancer of the mouse in all other kinds of cancer. But we have to assume that the internal secretion of the ovary is substituted in other cases by other variable factors, which may be either internal secretions of a different kind or external stimulations. The latter play, as is well known, a very important rôle in the origin of cancer. They represent in addition a quantity which can be increased at will in contradistinction to the internal secretions and other inner factors. Thus through the use of external stimulation it may be possible to increase at will the cancer rate in certain kinds of cancers; in this way the hereditarily fixed intensity may become entirely obscured. Yet it can not be doubted that after all this factor is present even in these latter kinds of cancer, the best representative of which is perhaps the Roentgen ray cancer in man.

7. Thus it has become possible to express in a quantitative way the tendency to a disease, cancer. This tendency is due to the interaction of two main factors, both internal, the one hereditarily fixed and the other accessible to experimental variation. Both factors combined are more than the predisposition to cancer; they are in the case of this particular kind of cancer its essential cause. There may be, as we have seen, other factors superimposed upon these primary factors, like the effect of pregnancy; but they are not necessary, and the first two factors suffice for the development of mammary cancer in

the variable numbers which are characteristic of the different strains of mice.

8. Is it possible to associate the hereditary tendency to cancer with the other factors characteristic of particular individual mice or of strains of mice? We found in certain cases that from main strains substrains could be detached which differed from the main strain not only in color, but also in the tumor rate; the most noteworthy cases of this kind are the English Silver and Silver Fawn substrains, detached from the main English strain at an early period of inbreeding. In this case the tumor rates differed in a very pronounced manner from that of the main strain. But the connection between color and cancer rate or age is in this case, as in some other cases, an accidental linkage. There is no real causal connection between the color and the factors that determine cancer. It is apparently similar in the case of other characters such as vigor, prolificity, size and rapidity of growth. We find strains of all kinds among the high as well as the medium and low rate tumor mice. This comes out quite clearly in the case of the various English-Cream hybrids. Here the tumor rate and age may be quite similar, namely, intermediate in different crosses, and yet some of these strains may be vigorous, others frail; some prolific, others poor breeders. In crosses certain characteristics, such as wildness or tameness, vigor and resistance to disease, or frailty, prolificity or the opposite, are inherited, just as the cancer rate and the cancer age; but these characters may be distributed among the hybrids independently of the predisposition to cancer. However, it so happens that some of the most prominent low rate tumor strains are poor breeders, slowly growing, although vigorous mice, while some of the high rate tumor strains are prolific, more rapidly growing; but this relation does not seem to hold good in all cases and may therefore not be causal. Quite recently T. B. Robertson observed among his mice that especially the rapidly growing individuals were prone to become cancer-

ous and he believes that a causal connection between the developmental rate and tendency to cancer exists.

9. There may, however, possibly be an exception to this independence of the hereditary transmission of the tendency to cancer. As we have stated, we arranged our various strains of mice in three groups, in strains with a high, with a medium and low tumor incidence, and we found that in these three groups the cancer age varies *pari passu* with the decrease in cancer rate. If we now determine in these same three groups on the same percentage basis the age of death from all other causes taken together except cancer, we find the differences between the three groups considerably less than if we compare the percentages of the cancer age. There is, however, a distinct difference. In the group of the high cancer rate strains the age of death from all other causes but cancer is decidedly earlier than in the medium and low rate cancer strains. The difference between the medium and low cancer rate strains is very slight, very much less than that between the high and medium rate tumor strains, but this slight difference is again in the same direction. This relationship between cancer rate and age of death from other diseases may be explained in two ways: (*a*) We may assume that the mice dying from cancer are the strongest, most resistant individuals of the family or strain and those which are left back are therefore relatively less resistant to disease; the higher the cancer rate in a strain, the less resistant are the mice not dying from cancer, and the earlier, therefore, their age of death from other causes. Or (*b*) the majority of the strains in which the cancer rate was high happened to be less resistant strains and therefore the average age of death from other diseases is earlier. The average difference between the medium and low rate tumor strains, as far as general power of resistance is concerned, happened to be very small. Although it is perhaps impossible to decide definitely between these alternatives, we believe the second one to be much more

probable. If the first alternative were correct, we should expect to find a decided difference also between the age of death from other causes than cancer in the medium and low cancer rate strains. Here the difference is almost negligible. Furthermore, there are some strains with a very high tumor rate, but in which the rate of death from cancer in the first age period is relatively small. In those strains the resistant individuals would therefore be spared by cancer in the first age period; thus the resistant individuals would not be eliminated and the age of death from other causes should accordingly be late in these strains. Actually we find in such high tumor rate strains an early age of death from other causes. We may therefore conclude that in the material on which we base our conclusions the large majority of the high rate tumor strains were strains with a low general resistance to disease. While, as we have stated above, a high or low degree of resistance may be associated with either a high, a medium or a low cancer rate, this association of a low degree of resistance with a high cancer rate in a prepondering number of strains may possibly be more than a coincidence. Maud Slye states that cancer strains are the strongest strains, a conclusion at variance with our experience.

10. The tendency to die from other causes than cancer at a certain period of life, the resistance to disease in general, is also hereditarily transmitted, but as we have stated above it varies among different groups of strains much less than the predisposition to cancer. This should be expected if we assume that there exists besides a general power of resistance a special resistance or predisposition to individual diseases, and that the latter may vary among different strains and may thus to a certain extent balance each other in various strains.

Again the tendency to die from other diseases than cancer at a certain period of life depends upon the cooperation of the generative organs; but while in the disposition to mammary cancer the internal secretion of

the ovary is the main factor and suspension of breeding plays only a subordinate rôle, in the case of resistance to other death producing conditions, the suspension of breeding seems to be the main factor and the elimination of the ovarian function only a subsidiary factor which merely acts through the suspension of breeding which it calls forth or in which at least the suspension of breeding is by far the more significant factor. We found that the differences in the tendency to die from other causes than cancer which we observe normally between different strains of mice are entirely or at least to a great extent eliminated in mice which are prevented from breeding. All those strains in which breeding is prevented become long lived. If a difference in the duration of life should still exist between different non-breeding strains, it must be very much smaller than that between breeding strains. Furthermore, the difference in the longevity between non-breeding mice and castrated mice is likewise very small and this is the reason why we conclude that castration prolongs the life of mice mainly through its effect on breeding. As far as the cancer rate is concerned, on the other hand, we have shown that castration at an early age is much more effective than prevention of breeding.

11. In man it has been observed by several authors that in older individuals suffering from cancer a multiplicity of slight malformations, often due apparently to a misplacement of embryonal tissue, or a multiplicity of benign, or rarely even of malignant, tumors could be observed. Similar observations were made more recently by Goodpasture in the case of old dogs. It is usual to attribute these findings either to an inherited tendency to tumor formation in general in which imperfections in embryonal development play a certain part, and in which, as a result of this general tendency, various kinds of tumors develop in the same individual in its old age, or by some authors emphasis is laid on the importance of old age as such in the etiology of cancer; old age is sup-

posed to bring about a multiplicity of tumors or corresponding malformations.

In a similar manner Maud Slye states there is in mice inherited a general tendency to cancer. In hybrid strains, according to this author, this general tendency finds expression in the first hybrid generations in a tendency to develop sarcoma, while in subsequent generations more specialized tissues are affected which develop into carcinoma, and in still later generations multiple tumors are prone to appear.

We have not been able to observe such a cycle in our strains of mice. We had uniformly in all generations to deal with mammary carcinoma and in many autopsies which we made of tumor mice we failed to observe other kinds of tumors. This does not exclude the possibility or even probability that occasionally lesions may have been present in other mice which were tumors of a different kind. We described, for instance, a beginning squamous cell carcinoma in a mouse afflicted with a mammary cancer about 10 years ago; but on the whole such occurrences were rare and they could not be interpreted as due to the inheritance of a general tendency to cancer; in each case external factors would then at least partially determine which particular expression this general tendency should find.

In our strains there was inherited essentially, not a general tendency to tumor formation, but a specialized tendency to cancer of the breast. This does not exclude the possibility that in certain strains a tendency to the development of another kind of tumors may have been inherited side by side with the tendency to mammary cancer. In favor of this conclusion we may cite the experiences in cases of the so-called endemic occurrence of cancer, as, for instance, the cancer of the inner canthus of the eye in cattle observed by us in 1899, the cancer of the scrotum in the rat observed by Hanau, our observations of sarcoma of the thyroid gland in the rat. All these are instances of the inheritance of specific kinds of cancers.

The most striking confirmation of this view has in recent years been funished by Miss Slye, who discovered certain families of mice in which a tendency to special cancers, as, for instance, cancer of the liver, was inherited. We therefore conclude that inheritance to cancer consists in general in a tendency to the inheritance of a particular kind of cancer. This agrees also with the results of Miss Stark, who found in *Drosophila* two specific kinds of inheritable, tumor like formations originating by mutation.

12. Our continued investigations have thus borne out our earlier conclusion that the endemic occurrence of cancer among animals is due to this hereditary transmission of the disposition to cancer. In addition, infection with certain metazoon parasites which act as an external stimulus comparable to the action, for instance, of Roentgen rays, may play a part in certain cases; but even here the metazoon parasites seem to act on a basis of hereditarily transmitted disposition. The observations of Fibiger, with which the recent findings of Rohdenburg are in agreement, suggest this conclusion.

13. While these statements apply directly only to animals, the evidence on hand makes it probable that, in principle, conditions are similar in man; here also in all probability one or more factors are hereditarily transmitted which determine the intensity in the tendency towards cancer development. In man this tendency has, however, in many cases been more or less equalized among different families as a result of long continued cross breeding (10). Wherever this factor can be eliminated as among different races which remained relatively pure or among a very stationary population, as in certain parts of Norway, the evidence points to the conclusion that here too marked differences in the tendency towards cancer exist in various strains and races (11). Even among the ordinary population some occasional striking findings very strongly suggest this view.

Furthermore, Davenport (12) has shown that the tendency to neurofibromatosis is hereditarily transmitted as

a dominant. Similarly, the tendency to certain other tumors is undoubtedly inherited. The recent statistical studies of C. C. Little make it very probable that an inherited predisposition to cancer plays a part in human cancer in general (13).

As to the increase in the cancer rate which seems to be so general an occurrence, we may suggest that, so far as it is not due merely to improved diagnosis, it could be referred to a greater frequency in the dominance of the parent with a tendency to a higher tumor rate in the offspring.

As we stated above, such a condition of dominance was observed among our hybrid strains.

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